Diverse sources of hippocampal unitary inhibitory postsynaptic potentials and the number of synaptic release sites

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Dual intracellular recordings from microscopically identified neurons in the hippocampus reveal that the synaptic terminals of three morphologically distinct types of interneuron act through $GABA_A$ receptors. Each type of interneuron forms up to 12 synaptic contacts with a postsynaptic principal neuron, but each interneuron innervates a different domain of the surface of the postsynaptic neuron. Different kinetics of the postsynaptic effects, together with the strategic placement of synapses, indicate that these GABAergic interneurons serve distinct functions in the cortical network.

THE excitatory neuronal network in the hippocampus is controlled by inhibitory innervation that governs the threshold of activation[1–4], pattern of action potential firing[5–7], and modification of synaptic strength[8]. Such inhibition is largely mediated by fast-spiking, local-circuit cells that release GABA (γ-aminobutyric acid)[4,7,9–12]. In anatomical terms there are many different kinds of GABAergic neuron[13–15], following several governing principles in their organization. First, the dendritic architecture of local-circuit cells reflects the spatial availability of afferent input[16]. Second, the axons of GABAergic cells vary with respect to targeting different domains on the surface of their respective postsynaptic target cells[14,16–18]. Third, the axonal terminal field of local-circuit cells may be precisely co-aligned with afferent excitatory inputs[16–18]. Although the latter features would suggest that it is the output, or, in physiological terms, the postsynaptic effect that is a key to the functional significance of interneurons, little is known as to which particular types of neuron mediate different inhibitory effects, such as recurrent inhibition[1,2,6], population synchronization, or shunting of dendritic excitatory inputs[19].

By combining electron microscopic analysis of synaptic connections with paired intracellular recordings from each of three distinct types of GABAergic cells and their respective postsynaptic principal neurons, we have found that each class of inhibitory neuron (axo-axonic, basket and bistratified cells) target different regions on the surface of principal neurons. Each type of inhibitory neuron forms between 6–12 synapses with an individual principal cell and each elicits short-latency inhibitory postsynaptic potentials (i.p.s.ps), but with different dynamic characteristics. GABA release from basket and axo-axonic terminals appears to be modulated by presynaptic $GABA_B$ receptors, whereas their postsynaptic effects are mediated by $GABA_A$ receptors.

Diversity of interneurons and synaptic output

Intracellular recording and subsequent visualization of fast-spiking neurons with somata located in the cellular layers of the hippocampal formation revealed distinct stereotyped patterns of axonal and dendritic arborizations. Basket cells ($n=31$ CA1; $n=3$ CA3; $n=5$ dentate gyrus (DG)) had most of their axon

TABLE 1 Location of synaptic release sites made by inhibitory cells on simultaneously recorded postsynaptic principal cells

Presynaptic inhibitory neuron	Location of release sites on a synaptically coupled postsynaptic cell					Overall random synaptic target pattern				
	Type	Soma	Dendrite	Axon	Total	Soma	Dendrite	Spine	Axon	Total
1. Basket cell, CA1 (Fig. 1)	Pyramidal cell	5	5	0	10	19 (44%)	24 (56%)	0	0	43
2. Basket cell, CA1,	Pyramidal cell	5	7	0	12	15 (45%)	18 (55%)	0	0	33
3. Bistratified cell, CA1 (Fig. 2)	Pyramidal cell	0	6*	0	6*	4 (3+8%)†	27 (78%)	4 (11%)	0	35
4. Axo-axonic cell, DG (Fig. 3)	Granule cell	0	0	8	8	0	0	0	33 (100%)	33
Pooled data (incl. 1–4)						Soma	Dendrite and spine		Axon	Total
Basket cells ($n=8$)	Pyramidal cells					79 (50.6%)	73 (46.8%)		4 (2.6%)	156
Bistratified cells ($n=2$)	Pyramidal cells					4 (2+6%)†	45 (92%)		0 (0%)	49
Axo-axonic cells ($n=4$)	3 p.c., 1 g.c.‡					6 (7%)	2 (2.5%)		76 (90.5%)	84

* Light microscopic estimate, three confirmed with EM.
† One on a pyramidal cell, three on a GABA-positive cell.
‡ p.c., pyramidal cell; g.c., granule cell.

terminals in the cellular layers (Fig. 1*C*). Electron microscopic analysis of a random sample of synapses ($n=156$) showed that they make synaptic contacts predominantly on somata (50.6%) and proximal dendrites (46.8%) of pyramidal cells (Table 1). In contrast, a cell that we term the bistratified cell ($n=11$, CA1) had relatively few terminals in the pyramidal cell layer of the hippocampus and extensively ramified in stratum radiatum and oriens (Fig. 2*B*), some axonal arbors covering the whole depth of stratum oriens and radiatum. Electron microscopic analysis of the efferent connections showed that of those synapses established on pyramidal cells, only 2% were on the soma and 98% on their dendrites (Table 1). Axo-axonic cells ($n=11$, CA1; $n=2$, CA3; $n=5$, DG) formed synapses exclusively or predominantly (90.5%; $n=84$ synapses examined) on the axon initial segment of principal cells (Figs 3*C*, 4*d*). Basket and axo-axonic cells have been shown to contain GABAergic markers[20,21] and in the absence of physiological verification, were thought to be inhibitory. As bistratified cells constitute a novel cell type we tested the GABA content of nine terminals of an intracellularly recorded cell by immunocytochemistry. All terminals were strongly GABA-positive (Fig. 4*f*). Finally, apart from the majority of selective cell types described above, a small proportion of cells ($n=6$) with transitional anatomical properties were also found in the CA1 area.

Sources of $GABA_A$-receptor-mediated i.p.s.ps

The synaptic effect of the three types of presynaptic GABAergic cells ($n=14$) was determined in paired recordings with postsynaptic pyramidal or granule cells ($n=28$), followed by the anatomical definition of the cell types and in several instances the synaptic connections (Table 1). All three cell types evoked short-latency i.p.s.ps, with rise and decay kinetics broadly similar to $GABA_A$-receptor mediated synaptic potentials (Figs 1*A*, *B*, 2*A* and 3*A*). At membrane potentials between −65 and −50 mV, i.p.s.ps were hyperpolarizing with reversal potentials (either directly determined or extrapolated) ranging between −65 and −78 mV, indicating that chloride is probably the major charge carrier[22]. The i.p.s.ps evoked by axo-axonic and basket cells (Figs 1*Ab*, *Bb* and *c*, and 3*Ab*) had short latencies (<2 ms from the peak of the presynaptic action potential) and fast rise times, demonstrating that, with respect to receptor type, the axon initial segment is similar to the somatic membrane, where $GABA_A$-receptor-mediated responses dominate[23]. Indeed, pharmacological experiments with GABA-receptor blockers (Fig. 5) demonstrate that the release of GABA from presynaptic terminals of axo-axonic cells and basket cells activates $GABA_A$-receptors in the postsynaptic membrane (Fig. 5*Ad* and *Bd*), whereas presynaptic $GABA_B$ receptors regulate transmitter release at these terminals (Fig. 5*Ac* and *Bc*). It appears that both axo-axonic and basket cells can be the joint source of the prominent i.p.s.ps recorded in the cellular layers of the hippocampus and postulated to be produced by synapses at or near the somata of principal cells[2,5]. Moreover, both i.p.s.ps are compatible with the time course of recurrent inhibition. Indeed, the electrophysiological (Fig. 1*Ad* and *E*) and anatomical (Figs 1*E* and 4*c*) demonstration of reciprocal synaptic connections between one of the basket cells and a pyramidal cell verifies the hypothesis[2,6] that the basket cell is involved in recurrent inhibition.

A source for pathway-specific inhibition

In contrast to the other cell types, the i.p.s.ps elicited by bistratified cells ($n=4$ postsynaptic pyramidal cells) were of dendritic origin with considerably longer rise and decay parameters. Basket cell i.p.s.p. ($n=11$ postsynaptic pyramidal cells) rise-times (10–90%) were, on average, 4.7 ± 2.2 ($\pm$s.d.) ms versus 13.8 ± 5.6 ms for those evoked by bistratified cells, and i.p.s.p. durations at half-amplitude were 34.2 ± 21.9 ms versus 67.1 ± 20.7 ms, respectively. Both parameters were significantly different ($P<0.05$; Mann–Whitney *U*-test). Although the slower kinetics of the i.p.s.ps evoked by the bistratified cell may reflect the more distal placement of the synaptic release sites (considered here as the functional equivalent of synaptic junctions; the term 'bouton' generally denotes a vesicle-filled axon terminal of presynaptic cells) and therefore some degree of electrotonic attenuation (Fig. 2*C*), recent data[24] would additionally suggest the presence of a different subset of $GABA_A$ receptors in the dendritic region. A separate source of GABA released from bistratified cells at proximal dendritic receptors may thus provide a mechanism for pathway-specific control of excitatory inputs[16,17,24], for example through dendritic shunting[19]. This hypothesis is supported by the co-alignment of the GABAergic bistratified cell axon with the glutamatergic Schaffer collateral input to the dendrites of pyramidal cells. As bistratified cells are strongly activated by Schaffer collaterals (data not shown), the release of GABA to dendrites will spatially and, to some extent, temporally coincide with the release of glutamate from Schaffer collaterals. Therefore it may be predominantly dendritic inhibition that will lead to an increase in the dynamic range of excitatory inputs[17,25].

Basket-cell-evoked post-inhibitory facilitation

Some degree of variability of averaged postsynaptic responses has been noted which was also attributed to different types of presynaptic cells[10]. The difference seen here in responses to basket and bistratified cells provides evidence for this assumption. However, we also found variability in the averaged responses of different cells postsynaptic to the same presynaptic inhibitory cell. For example, i.p.s.ps elicited by the same presynaptic basket cell in different pyramidal cells could either slowly decay back to baseline or display post-inhibitory facilitation (3 out of 15), which could be of sufficient amplitude to trigger action potentials (Fig. 1*Bb*, *c* and *f*). Depolarizing potentials have been reported in response to GABA application to the dendritic region of pyramidal cells[26], and they are thought to be due to a more positive chloride equilibrium potential at the dendrites compared to the soma[27]. In light of the proximal placement of basket cell synapses, as well as the more distal position of the bistratified synapses, other mechanisms may underlie the depolarizing responses evoked by basket cells. Regardless of the ionic mechanism responsible for evoking post-inhibitory facilitation, the estimated (see below) convergence of 25 basket cells acting together on a single pyramidal cell may suffice to trigger rebound firing.

Several release sites mediate unitary i.p.s.ps

Evidence for the monosynaptic nature of the connections was obtained by electron microscopy, which also revealed the precise number of synaptic release sites responsible for postsynaptic responses (Fig. 4 and Table 1). Two basket cells made 10 and 12 synaptic junctions respectively and one axo-axonic cell made 8 junctions on a single postsynaptic cell. Moreover, single presynaptic boutons may establish multiple synaptic release sites, raising the question of whether transmitter release at these sites is independent. In the case of the bistratified cell, following light microscopic prediction of six contacts, three out of three tested contacts were verified by electron microscopy to confirm the correctness of such an estimate.

In addition to multiple innervation from individual inhibitory cells, the postsynaptic cells also received substantially more synapses from non-labelled boutons which were similar to the identified ones, indicating convergence of inhibitory cells. Continuous serial sectioning of the postsynaptic cells for electron microscopy showed that the pyramidal cell postsynaptic to basket cell no. 2 received 119 synaptic contacts on the soma, in addition to the five made by biocytin-filled terminals. Provided that all these synapses were made by similar basket cells, approximately 25 basket cells may converge on a single CA1 pyramidal cell. Likewise, the axon initial segment of the granule cell (Fig. 3*B*) received forty synapses in addition to the eight made by biocytin-filled terminals (Figs 3*C* and 4*d*). This indi-

cates that about six axo-axonic cells converge on one granule cell.

Discussion

Dual recording and labelling experiments revealed that three distinct types of hippocampal GABAergic interneurons elicit short-latency i.p.s.ps in postsynaptic principal cells. Recurrent collaterals of the latter evoke monosynaptic e.p.s.ps in pyramidal[28] and local-circuit cells[28–30]. In striking contrast to the recurrent pyramidal-to-interneuron connections, which are mediated by one synaptic junction[30] (Figs 1*E* and 4*c*), inhibitory unitary interactions are generally mediated by multiple synaptic release sites, a finding that may also explain the safety of transmission, as evident from the rarity of apparent transmission failures[7,10]. Pharmacological data of unitary interactions suggest that at least basket and axo-axonic cells evoke their postsynaptic effects solely through $GABA_A$ receptors, thus suggesting synaptic segregation of $GABA_A$ and $GABA_B$ receptors on the surface of postsynaptic cells[4,31–33].

The results reveal a division of labour among inhibitory interneurons which not only use the same transmitter, GABA, but also act through similar postsynaptic receptor mechanisms.

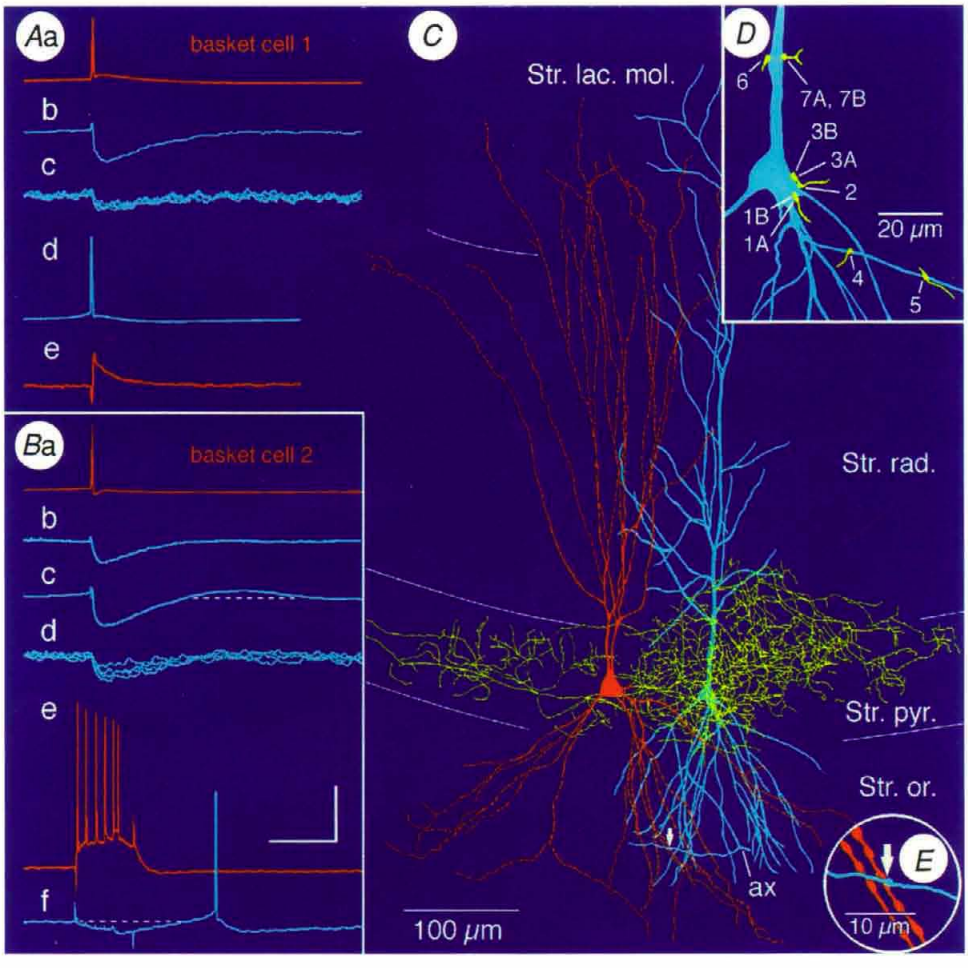
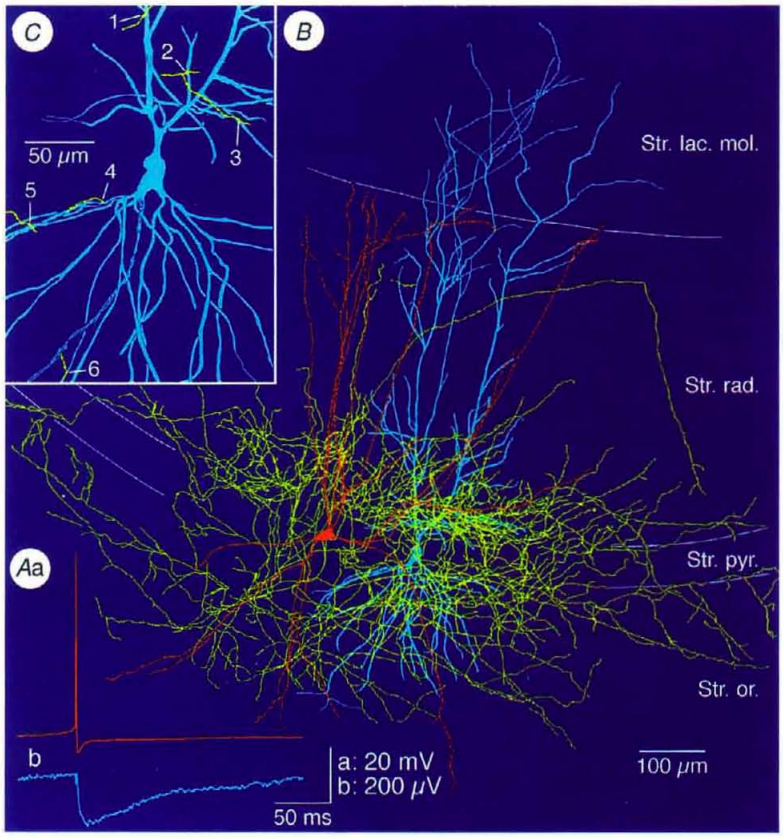


FIG. 1 Postsynaptic effect of basket cells and location of synaptic release sites on a pyramidal cell in the CA1 area. In Figs 1–3, the soma, dendrites and intracellularly recorded membrane potential of presynaptic inhibitory cells is shown in red, their axon in yellow, and the synaptically coupled postsynaptic principal cell and its membrane potential in blue. *A, B*, Two identified basket cells (Table 1) elicit short-latency i.p.s.ps in postsynaptic pyramidal cells (*Ab* and *c*; *Bb–d, f*). Individual i.p.s.ps showed considerable amplitude fluctuation (*Bd*) and varied between the level of detectability and 2 mV. The amplitude of averaged basket cell i.p.s.ps ranged between 310 and 920 μV and was correlated with the membrane potential of the postsynaptic cell. In basket cell 1 (shown in *C* and *D*) the i.p.s.p amplitude declined linearly between −50 and −60 mV and response reversal was extrapolated to −65 mV. Interestingly, i.p.s.ps could either decay back to baseline (*Ab, Bb*) or, alternatively, showed a depolarizing overshoot (*Bc*) of sufficient amplitude to trigger action potentials (*Bf*). The postsynaptic pyramidal cell illustrated in *C* and *D* elicited a reciprocal short-latency e.p.s.p. (amplitude 660 μV) in the presynaptic inhibitory basket cell 1 (*Ae*), demonstrating that basket cells participate in recurrent inhibitory circuits. The traces in *Aa, b, d* and *e* and *Ba–c* represent averages of >100 sweeps. *C*, Most of the axon of this basket cell (no. 1 in Table 1) is restricted to the pyramidal cell layer (Str. pyr.), resulting in a general target profile rich in axo-somatic synaptic release sites, also demonstrated at the single cell level in *D*. *D*, Location of 10 synaptic junctions (see Fig. 4 for example) by electron microscopy, received by the postsynaptic pyramidal cell shown in *C*, giving the postsynaptic effect shown in *Ab*. Three boutons (numbers 1, 3 and 7) made 2 synaptic junctions each. *E*, Enlargement of the area labelled by small arrow in *C*, showing a recurrent collateral of the pyramidal cell axon (ax) which is in contact with a basket cell dendrite. Subsequent electron microscopy revealed that a single synaptic release site (arrow; also shown in Fig. 4*c*) mediated the recurrent e.p.s.p. shown in *Ae*. Str. lac. mol., stratum lacunosum moleculare; Str. rad, stratum radiatum; Str. or., stratum oriens. Scale bars in *A* and *B*: *Aa, d* and *Ba*: 40 mV; *Be* and *f*: 20 mV; *Ac* and *Bd*: 5 mV; *Ab, e* and *Bb, c*: 1 mV; *A* and *Ba–d*: 50 ms; *Be* and *f*: 100 ms.

METHODS. The slicing procedure has been described[40]. In brief, recordings were obtained in 400-μm-thick transverse hippocampal slices of adult (>150 g) female Wistar rats. Slices were maintained at 34–35 °C on a nylon mesh at the interface between oxygenated ACSF (in mM: 126 NaCl, 3.0 KCl, 1.25 NaH_2PO_4, 24 $NaHCO_3$, 2.0 $MgSO_4$, 2.0 $CaCl_2$, and 10 glucose) and a humidified atmosphere saturated with 95% O_2 and 5% CO_2. The flow rate was adjusted to 1.5 ml min^{-1}. Micropipettes were filled with 2% biocytin in 1.5 M KCH_3SO_4 and bevelled to a d.c. resistance ranging between 60–150 MΩ. Presumed interneurons were impaled using previously established physiological criteria[9,40]. When a stable recording was obtained, a search was made for synaptically coupled cells displaying the properties of hippocampal principal cells. Capacitive coupling between the recording electrodes was either eliminated off-line[10] or, alternatively, on-line using a modified Axoprobe amplifier. Synaptic coupling was tested using on-line averaging and injecting depolarizing current pulses into the presumed presynaptic cell, or injecting a constant depolarizing current which was adjusted to induce tonic firing at rates varying between >100 and 0.5 Hz. Diffusion of biocytin during most recordings usually resulted in adequate filling. Slices were processed for light and electron microscopy as before[16,40]. Recovered cells were reconstructed from serial 60-μm sections using a light microscope and drawing tube at 1,250 × magnification.

FIG. 2 Postsynaptic effect of a bistratified cell and location of contact sites on a pyramidal cell in the CA1 area. *A*, Action potentials (*Aa*) of this cell (Table 1, no. 3) elicited a small-amplitude, short-latency i.p.s.p. in a postsynaptic pyramidal cell (*b*). With linear regression, the i.p.s.p. reversal was extrapolated to −77 mV. *B*, Same bistratified/pyramidal pair as in *A*; note the relatively sparse inhibitory axon (yellow) in stratum pyramidale (Str. pyr.) and its increased density in the adjacent strata radiatum (Str. rad.) and oriens (Str. or.), where Schaffer collateral afferents from the CA3 area terminate. Dendrites of this cell type do not significantly enter into the stratum lacunosum moleculare (Str. lac. mol.) where the perforant path terminates. *C*, Location of 6 contact sites between the GABAergic axon (yellow; see Fig. 4) and the postsynaptic pyramidal cell. Only the dendrites were contacted, and axo-somatic synapses were also rare in the random sample of synapses (Table 1).



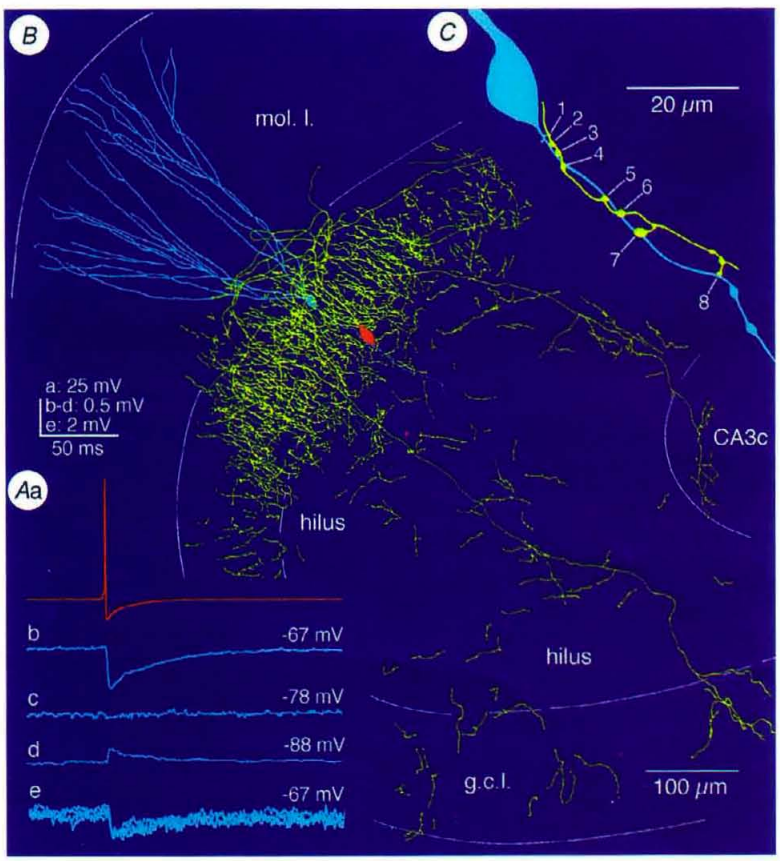
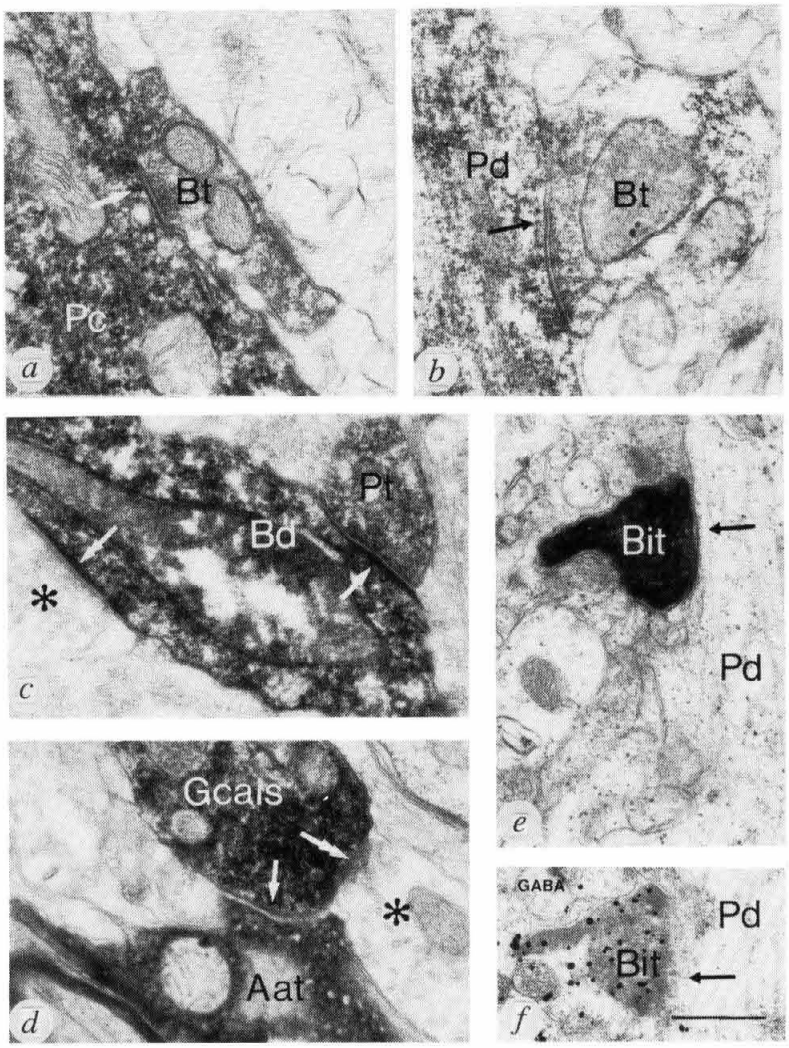


FIG. 3 Postsynaptic effect of an axo-axonic cell and location of 8 synaptic release sites on a granule cell axon initial segment in the dentate gyrus. *A*, At −67 mV, the presynaptic axo-axonic cell (*a*) elicited a short-latency fast i.p.s.p. (*b*). Individual i.p.s.ps fluctuated in amplitude, which could be up to 2 mV (*e*), whereas the average of all trials had an amplitude of 460 μV. The response reversed around −78 mV (*c* and *d*), but the *I/V* relationship of the i.p.s.p. was clearly nonlinear. *B*, The inhibitory axon (yellow) innervated most of the granule cell layer (g.c.l.), the hilus, and the tip of the CA3c area. The dendrites of this axo-axonic cell were not recovered, only the cell body giving rise to the axon is shown. The postsynaptic granule cell received synapses only on the axon initial segment and a random sample of synapses confirmed this high degree of target specificity (no. 4 in Table 1). *C*, Location of 8 synaptic junctions (Fig. 4*d*) that mediated the effect shown in *A*. mol., Molecular layer.

FIG. 4 *a* and *b*, Electron microscopic demonstration of physiologically identified inhibitory synapses (arrows) between presynaptic boutons of the basket cell (Bt) and the soma (Pc; cell shown in Fig. 1) or the apical dendrite (Pd; no. 2 in Table 1) of pyramidal cells; *c*, Recurrent excitatory synapse between the pyramidal cell terminal (Pt; cell shown in Fig. 1) and a basket cell dendrite (Bd). Note the asymmetric postsynaptic density. Asterisk denotes an unlabelled terminal which is in asymmetrical synaptic contact (double arrow) with the same basket cell dendrite. *d*, Inhibitory synaptic contact between a bouton of the axo-axonic cell (Aat; no. 5 in Fig. 3C) and the axon initial segment (Gcais) of the granule cell shown in Fig. 3; asterisk marks a converging terminal from another axo-axonic cell; *e* and *f*, Synaptic junction between a bouton (Bit) of the bistratified cell shown in Fig. 2, and a non-recorded pyramidal cell dendrite (Pd). The section in *f* is serial to that in *e* and shows that the bistratified cell bouton is immunopositive for GABA, as demonstrated by the high density of metal particles. Scale bar for all pictures, 0.4 μm.

METHODS. Resin-embedded cells were serially sectioned for electron microscopy and stained with lead citrate. Some sections were immunoreacted for GABA using a highly sensitive silver-intensified immunogold method[17] and a rabbit antiserum to GABA[41]. Synaptic contacts were identified on the basis of the rigid apposition of pre- and postsynaptic membranes, the electron-dense cleft material and the postsynaptic density, when detectable.



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The scale bar for all panels of Fig. 4 of this Article was 0.4 μm, and not 0.2 μm as published.

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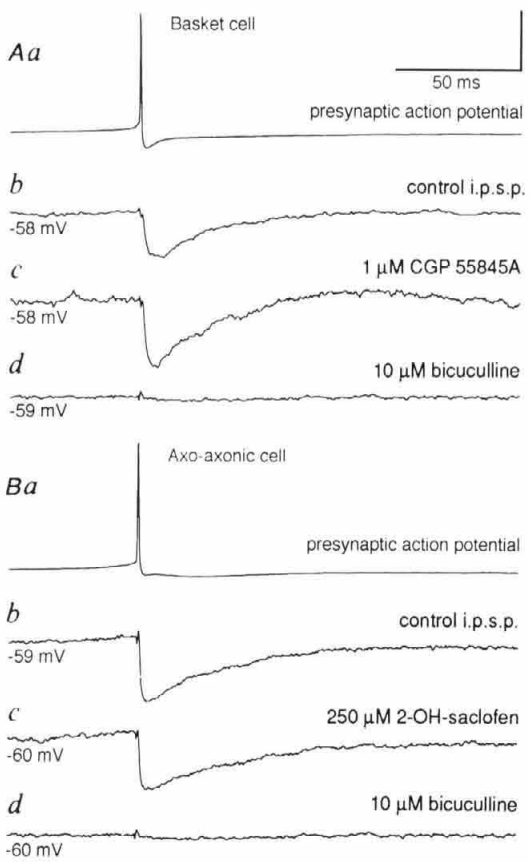

FIG. 5 Effect of GABA receptor antagonists on unitary i.p.s.ps in the CA1 region. *A*, A presynaptic CA1 basket cell (*a*) elicited a short-latency i.p.s.p. (*b*) in a postsynaptic pyramidal cell. Subsequent bath application of the non-NMDA receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX; 5 μM) and the NMDA receptor antagonist DL-2-amino-5-phosphonopentanoic acid (AP5; 30 μM) left the response unaffected (not illustrated). Following superfusion of 1 μM of the $GABA_B$ receptor antagonist CGP 55845A (ref. 42), the i.p.s.p.-amplitude increased by 33% (*c*), presumably as a result of an antagonist effect of CGP 55845A on presynaptic $GABA_B$ receptors[43]. Addition of 10 μM bicuculline methochloride to the superfusate virtually eliminated the response (*d*). Input resistance (42 MΩ) and time constant (11.4 ms) of the pyramidal cell were monitored throughout and remained stable. Scale bar (vertical): *a*, 25 mV; *b–d*, 0.5 mV. *B*, A CA1 axo-axonic cell (*a*) elicited a short-latency i.p.s.p. in a postsynaptic pyramidal cell (*b*). In the presence of 5 μM CNQX and 30 μM AP5, bath application of the $GABA_B$ receptor antagonist 2-OH-saclofen (250 μM) resulted in a 12% decrease of the i.p.s.p. amplitude (*c*). In view of the known slow onset of $GABA_B$-receptor-mediated postsynaptic mechanisms[44], this effect on the early phase of the i.p.s.p. is probably due to a partial agonist action of 2-OH-saclofen on presynaptic $GABA_B$ receptors[45]. A −1 mV change of the membrane potential during the recording may have also contributed to the amplitude decrease of the i.p.s.p. Subsequent perfusion with 10 μM bicuculline methochloride eliminated the response (*d*). The input resistance of the pyramidal cell at the beginning and end of the experiment remained unchanged (24 MΩ). All traces represent averages of >100 sweeps. Scale bar (vertical): *a*, 25 mV; *b–d*, 0.5 mV.

However, kinetic differences of the postsynaptic effects, as well as the anatomical segregation of release sites, indicate that $GABA_A$ receptor properties, as well as the placement of synaptic release sites, play a role in the functional differentiation of inhibitory neurons. In this respect, the strategic location of $GABA_A$ receptors on the axon initial segment, where the action potential threshold is lowest[34], predestines axo-axonic cells to govern the firing threshold, as suggested earlier on anatomical and physiological grounds[35,36]. Basket cells not only mediate recurrent inhibition, they also evoke rebound firing and, by virtue of their divergence to hundreds of pyramidal cells, may be an effective means to synchronize principal cell activity, as predicted on theoretical grounds[37]. In the living animal, such $GABA_A$-receptor-mediated mechanisms are involved in rhythmic membrane potential changes, which may result in the phase-locking of large numbers of principal cells[38]. In contrast to axo-axonic and basket cells, the bistratified input discovered here is selectively associated with a major glutamatergic input, the Schaffer collateral/commissural pathway. This selective alignment of GABAergic synapses with particular excitatory afferents on the same dendritic segments was previously found in the dentate gyrus[16,17] and also in the CA3 region[18]. This spatial coincidence provides a selective mechanism for bistratified cells to carry out a downward re-scaling of Schaffer collateral/commissural e.p.s.ps in pyramidal cells. Differences in function may therefore be the key to explain the diversity of cortical interneurons[39]. □

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